

The Efficacy and Safety of PSD503 (Phenylephrine 20% w/w) for Topical Application in Women with Stress Urinary Incontinence. A Phase II, Multi-Centre, Double-Blind, Placebo-Controlled, Cross-Over Study

Cardozo L¹; Abrams P²; Robinson D¹; Ellis-Jones J²; Heath P³; Wyllie MG³

¹ Department of Urogynaecology, Golden Jubilee Wing, Kings College Hospital, Denmark Hill, London, SE5 9RS, UK;

² Bristol Urological Institute, Southmead Hospital, Westbury on Trym, Bristol, Avon, BS10 5NB, UK; ³ Plethora Solutions Limited, 233, High Holborn, London, WC1V 7DN

INTRODUCTION

PSD503 is a controlled dose topical gel, which contains the alpha-adrenergic agonist phenylephrine (20% w/w) and has been developed as a locally administered treatment for the symptoms of stress urinary incontinence (SUI).

It is applied to the anterior vaginal wall at the level of the internal urethral sphincter (approximately 3.5 cm proximal to the external urethral meatus) and along the external markings of the urethra (i.e. the area of the anterior vaginal wall from the level of the internal sphincter to the external urethral meatus).

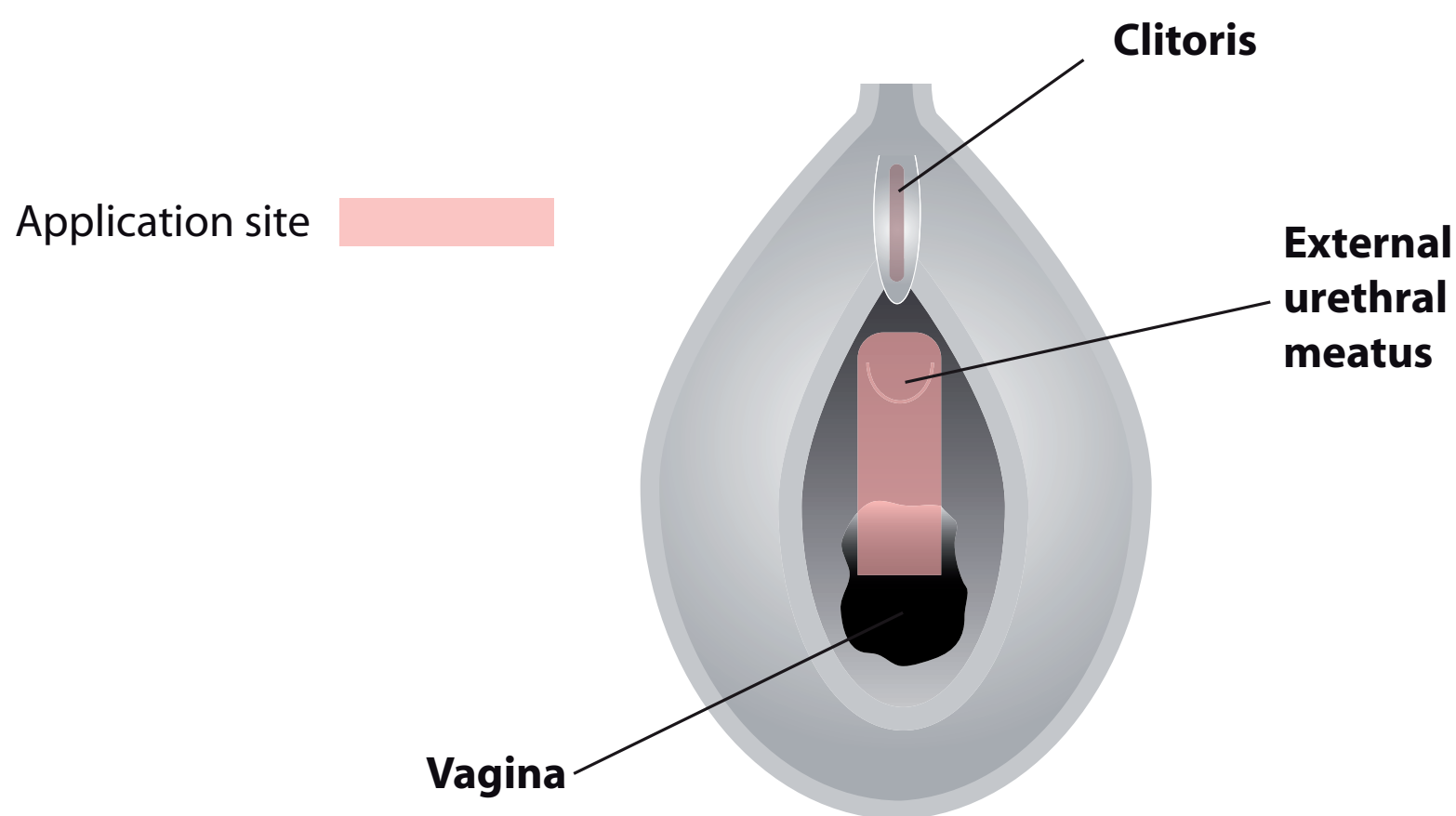


Figure 1: Site of treatment application

By applying the gel in this manner it is believed that sufficient phenylephrine may be absorbed transvaginally, to act on the urethra (so as to increase urethral tone) and the urethral sphincter thus providing symptomatic relief, without systemic side effects.

OBJECTIVES

The **primary objective** of this trial was to evaluate whether the topical application of PSD503 could be efficacious in improving symptoms of SUI. This was investigated by measuring the percentage change in pad weight gain following an exercise stress pad test, from pre-dose to post-dose. The exercise stress pad test was based on a modification of the one hour ICS exercise stress pad test for SUI [1].

Secondary objectives included:

- measurement of post-dose phenylephrine plasma concentrations
- evaluation of blood pressure and pulse rate
- assessment of the safety and tolerability of PSD503, as compared to placebo.

MATERIALS AND METHODS

The trial was a randomised, two-treatment, two-period crossover design, which enabled within-subject comparison of PSD503 and placebo. There was a 3-10 day washout period between treatment periods (Figure 2).

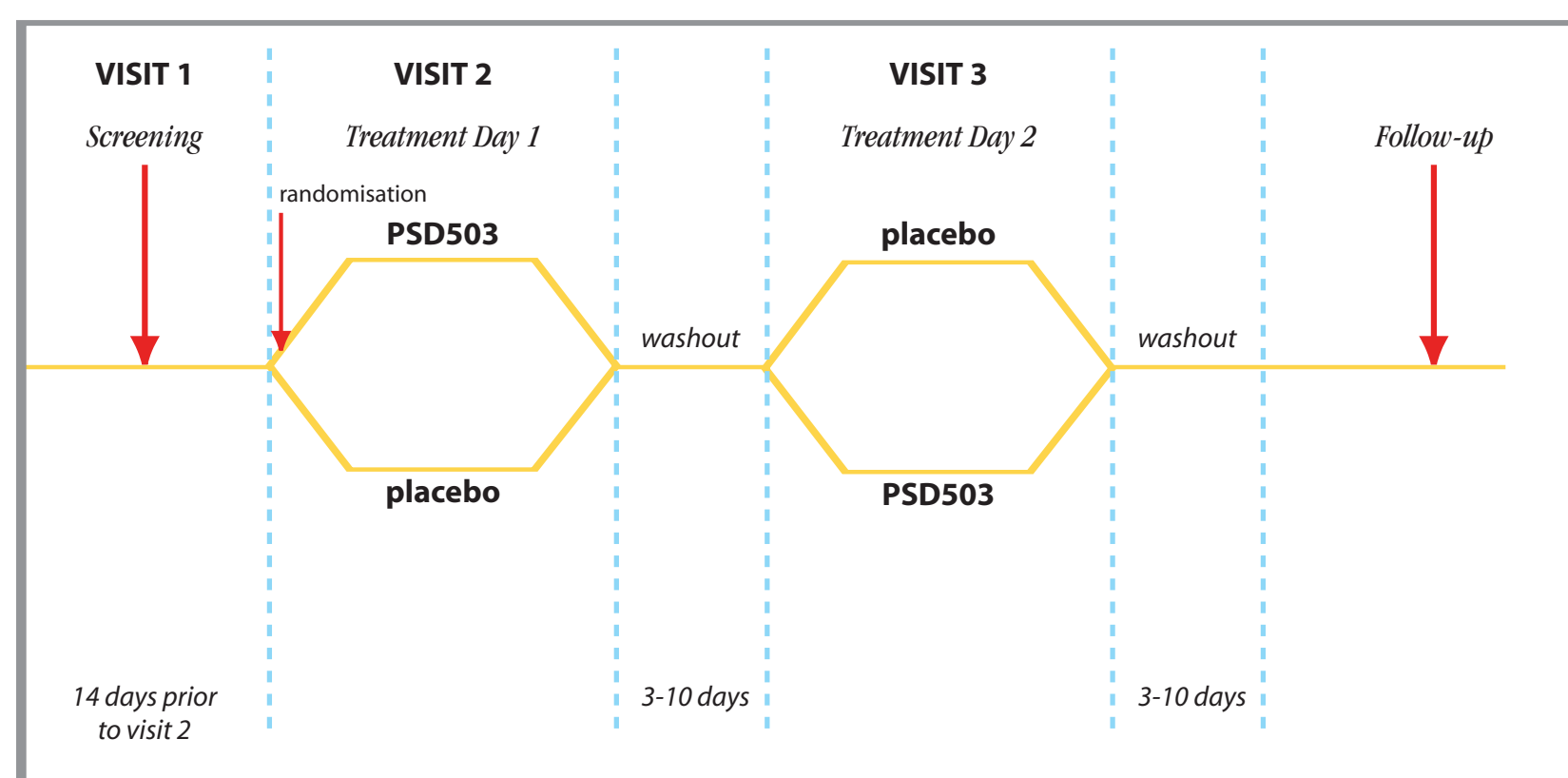


Figure 2: Study design

- Patients (n=12) with SUI, confirmed by a positive urinary stress test and urodynamic assessment (including normal filling cystometry) within 36 months of screening, and incontinence episode frequency ≥ 7 and ≤ 21 per week (as determined by a frequency volume chart) were included.
- On each treatment day, patients underwent a pre-dose exercise stress pad test, blood pressure and pulse assessment. A blood sample was taken to determine baseline phenylephrine plasma concentration.
- A single dose of 0.25 ml PSD503 or placebo was dispensed using a Metricap Closure, MetriCap (Pty) Ltd (a metered dose dispensing closure device for gels and creams) and applied as described. The exercise stress pad test was then repeated 2 hours post-dose.
- Blood pressure and pulse rate were measured at various time points over a minimum period of 3 hours post-dose.
- Phenylephrine plasma concentrations were quantified at one and three hours post-dose.
- The occurrence of adverse events (AEs) was reported throughout each study period and reviewed at Study Visit 2 and at the Follow-up Visit.

RESULTS

Summary of change in pad weight gain from pre-dose to post-dose				
ITT population (N=12)		Placebo	PSD503	
Pad weight gain (g)	Pre-dose	Median	22.0	39.0
		Range	3 to 179	1 to 74
	Post-dose	Median	15.5	9.5
		Range	0 to 113	1 to 42
Absolute change in pad weight (g) pre-dose to post-dose		Median	-10.0	-22.0
		Range	-115 to 25	-40 to 2
% Change *		Median	-38.00	-54.33
		Range	-100 to 357.1	-97.6 to 40.0

* % Change in pad weight gain from pre-dose to post-dose, calculated as: $100 \times ((\text{pad weight gain at post-dose}) - (\text{pad weight gain at pre-dose})) / (\text{pad weight gain at pre-dose})$

The median phenylephrine plasma concentrations (in the safety population, N=17) following treatment with PSD503 were:

Pre-dose	0.000 ng/ml
1 hour post-dose	1.490 ng/ml
3 hours post-dose	1.305 ng/ml

This finding was consistent with the observation that PSD503 did not elevate blood pressure or pulse rate in any of the subjects.

Treatment-related AEs (Safety population, N=17)			
		Placebo	PSD503
Gastrointestinal	Abdominal pain	0	1
	Constipation	1	0
	Diahorrea	1	1
General & administration site conditions	Application site pain	1	0
	Pyrexia	1	0
	Supra pubic pain	1	0
Hepatobiliary	Abnormal hepatic function	0	1
Nervous system	Headache	1	0
Infections	Cystitis	1	0
Renal & Urinary	Urethral pain	1	0
TOTAL		8	3

There were no cardiovascular AEs reported and all treatment-related AEs were classified as mild in severity. No subject withdrew due to an AE and there were no reports of serious adverse events or deaths.

CONCLUSIONS

This study demonstrated that:

- Treatment with PSD503 resulted in a greater reduction in pad weight gain than placebo, when expressed as both a percentage change (median: 54% vs. 38%) and absolute change (median: 22g vs. 10g) from pre-dose application.
- Only low levels of PSD503 applied to the anterior vaginal wall were absorbed into the bloodstream, with the highest concentration of phenylephrine detectable one hour post-dose application.
- PSD503 did not elevate blood pressure or pulse rate in any of the subjects and appeared to be well tolerated.

These results indicate that PSD503 may be an effective localised treatment to reduce the involuntary leakage of urine associated with SUI, avoiding the side effects associated with systemic administration of alpha-adrenergic agonists.

Reference

1. Abrams, P., et al: The standardisation of terminology of lower urinary tract function: the International Continence Society Committee on Standardisation of Terminology. Scan J Urol Nephrol, 1988. 114(suppl): p. 5-19.

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